PII-98

NO CLINICALLY SIGNIFICANT INTERACTIONS BETWEEN THE ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN AND AMIODARONE, ATORVASTATIN, OR DIGOXIN. H. Dorani, MSc, K. Schützer, MD, M. Wollbratt, MSc, T. C. Sarich, PhD, U. G. Eriksson, PhD, R. Teng, PhD, L. Ohlsson, MSc, E. Kessler, MSc, U. Wall, MD, I. Kalies, PhD, J. E. Hamer, MSc, AstraZeneca R&D Mölndal, AstraZeneca L.P., Mölndal, Sweden.

Background: The oral direct thrombin inhibitor ximelagatran has shown clinical benefit in patients with atrial fibrillation at risk of stroke. The potential for interaction of ximelagatran with amiodarone, atorvastatin, or digoxin, was assessed in 3 randomized studies in healthy volunteers. **Methods:** Study 1 was a placebo-controlled, parallel-group study (n=26) with ximelagatran (36mg) or placebo BID for 8 days and amiodarone (single 600mg oral dose) on Day 4. Study 2 was a crossover study (n=16) with atorvastatin (single 40mg oral dose) during one treatment period and ximelagatran (36mg BID for 5 days) plus a single dose of atorvastatin (40mg) on Day 4 during the other treatment period. Study 3 was a double-blind, crossover study (n=16) with ximelagatran (36mg) or placebo BID for 8 days and digoxin (single 0.5mg dose) on Day 4. **Results:** For melagatran, the active form of ximelagatran, AUC and C_{max} geometric mean ratios (90% CI) for combined therapy relative to monotherapy with either drug were within or only slightly outside predefined bounds for no interaction. Similarly, no relevant changes were observed for the AUC and C_{max} of amiodarone, atorvastatin, or digoxin. None of the coadministered drugs affected the concentration–effect relationship of melagatran on activated partial thromboplastin time. **Conclusions:** No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when ximelagatran was administered with amiodarone, atorvastatin, or digoxin.

PII-99

EFFECT OF ERYTHROMYCIN ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN AND ITS ACTIVE FORM MELAGATRAN. H. Dorani, MSc, K. Schützer, MD, T. C. Sarich, PhD, U. Wall, MD, L. Ohlsson, MSc, U. G. Eriksson, PhD, AstraZeneca R&D Mölndal, AstraZeneca L.P., Mölndal, Sweden.

Background: Ximelagatran (Exanta™, AstraZeneca), an oral direct thrombin inhibitor for the prevention and treatment of thromboembolic disorders, is rapidly absorbed and bioconverted to its active form melagatran. The metabolism of ximelagatran is independent of CYP450 enzymes and hence it has a low potential for drug interactions. This study evaluated the effect of erythromycin on the pharmacokinetics (PK) and pharmacodynamics (PD) of melagatran. **Methods:** An open, sequential, single-centre study in healthy volunteers (n=16; mean age 24 years, range 20-32 years) with ximelagatran 36mg on Day 1, then erythromycin 500mg TID on Days 2-5 followed by ximelagatran 36 mg plus erythromycin on Day 6. **Results:** For melagatran, AUC and C_{max} geometric mean ratios for combined therapy (Day 6) relative to monotherapy (Day 1) were 1.82 (90% CI, 1.64-2.01) and 1.74 (90% CI, 1.52-2.00), respectively, (n=15), falling outside of the predefined bounds for no interaction. Geometric mean ratios for t_{max} and $t_{1/2}$ of melagatran were 1.14 and 0.93, respectively. The erythromycin-associated elevation in plasma melagatran concentrations increased the peak activated partial thromboplastin time (aPTT) prolongation from 41s to 44s. Ximelagatran was well tolerated alone, and in combination with erythromycin. **Conclusions:** This study showed evidence of a pharmacokinetic interaction between ximelagatran and erythromycin with respect to melagatran PK, which is being investigated, but only a small effect on aPTT.

PII-100

DEVELOPMENT OF A PHARMACOKINETIC PHARMACODYNAMIC (PKPD) MODEL TO PREDICT ONSET OF HEMOLYTIC ANEMIA IN (PEG)INTERFERON/RIBAVIRIN TREATED HEPATITIS–C VIRUS (HCV)-INFECTED PATIENTS. B. Agoram, PhD, R. Marino, BS, S. George, MD, N. Lam, PharmD, A. Heatherington, PhD, Amgen, Inc., Thousand Oaks, CA.

Purpose: A significant side-effect of HCV treatment with interferon (IFN)/ribavirin (RBV) therapy is hemolytic anemia, which can result in RBV dose reduction and may compromise efficacy. Darbepoetin alfa (DA) is an erythropoiesis stimulating protein approved for the treatment of anemia associated with renal insufficiency and cancer. The goal of the current work was to use PKPD modeling to predict onset of anemia in HCV patients on antiviral treatment.

Methods: The PKPD model used was a physiologically based indirect response model wherein the erythropoietic agent's concentration stimulates production of erythrocyte progenitors. The model structure was modified to account for hemolytic anemia using a first-order rate equation, and subsequent up-regulation of endogenous erythropoietin using a Michaelis-Menten type equation. PD model parameters were obtained using hemoglobin (Hb) data from patients on antiviral therapy treated with rHuEPO, and then modified to allow predictions for DA.

Results: PKPD model simulations predicted that

1. about 60% of patients on antiviral therapy were likely to become anemic (Hb< 12 g/dL)
2. median time to onset of anemia was 4 weeks
3. 25% were likely to require RBV dose reduction (Hb<10 g/dL) if anemia was untreated.

Conclusions: PKPD modeling was useful in predicting onset of anemia in HCV patients undergoing antiviral treatment. The model aided in the design of a clinical trial to explore the use of DA to treat anemia due to antiviral therapy.

PII-101

LACK OF EFFECT OF APREPITANT (APR) ON THE PHARMACOKINETICS (PK) AND SAFETY OF PALONOSETRON (PALO). A. K. Shah, PhD, S. C. Gallagher, MS, L. Latimer, MS, M. T. Cullen, MD, T. L. Hunt, MD, PhD, MGI Pharma Inc, PPD Development LLC, Bloomington, MN.

Purpose: PALO is a potent and highly selective 5-hydroxytryptamine$_3$ receptor antagonist that has shown clinical efficacy for the prevention of both acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy. We evaluated the PK and safety of PALO with concomitant administration of APR, a neurokinin$_1$ receptor antagonist, in healthy subjects.

Methods: This was an open-label, randomized, two-period crossover study in 12 subjects. Subjects received Treatment A: a single dose of PALO 0.25 mg IV and with a 14-day wash-out period Treatment B: APR 125 mg oral dose followed 30 minutes later by PALO 0.25 mg IV with daily oral dosing of APR 80 mg continued on days 2 and 3.

Results: Mean PK parameters of PALO are summarized below.

Cmax (ng/L)	AUC(0-∞) (ng•hr/L)	T1/2 (hr)	CLp (mL/min)	Vdss (L)
		PALO without APR		
1700†	32900†	43.0	136	442
		PALO with APR		
1680†	33200†	40.0	130	411
98.6[$]	101[$]			
61.8, 157[¶]	85.6, 119[¶]	0.348‡	0.735‡	0.463‡

†Geometric mean, [$]%Ratio of geometric means, [¶]90% Confidence Interval, ‡p-Value for Treatment difference.

Conclusion: PALO was well tolerated, with no clinically significant changes in vital signs or laboratory tests. These results indicate that the PK and safety of PALO were not altered with coadministration of APR.